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Dopaminergic medication shifts the balance between going and stopping in Parkinson's disease

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ABSTRACT

The present behavioral study delineates the impact of Parkinson's disease (PD) and of dopaminergic medication on action control over voluntary behavior. Previous studies reported either prolonged responding or stopping latencies in PD compared to healthy controls (HC). Few studies investigated the effects of dopaminergic medication on these processes concurrently. We administered a stop-change task, an extended version of the stop task, that required (i) speeded responding to a go signal (i.e., going), (ii) inhibiting ongoing motor responses (i.e., stopping), and (iii) changing to an alternative response. PD performance (n = 33) was collected once during regular dopaminergic medication conditions (On state) and once after a medication washout period (Off state). A group of age-matched HC (n = 21) performed the stop-change task once. Response latencies to go signals were comparable between HC and PD Off, indicative of unimpaired going. Compared to HC, PD Off showed prolonged stopping latencies. Within the clinical group, stopping latencies significantly improved after taking dopaminergic medication. Interestingly, the shorter stopping latencies observed in the On state were paralleled by longer response latencies to go signals. The degree of the inhibition improvement observed in the medication state was correlated with the degree of response slowing. Change RT did not vary between groups or between medication states. These patterns of results are discussed in terms of a tradeoff between going versus stopping of motor responses in PD patients. Shifts of this tradeoff seem to be driven by dopaminergic medication, which has potential clinical implications.

1. Introduction

A cardinal feature of Parkinson's disease (PD) is bradykinesia, observed clinically as slower initiation and execution of a range of actions such as rising from a chair, walking a corridor, turning or circumnavigating obstacles, performing repetitive sequences of upper or lower extremity movements, and making postural adjustments in response to gait perturbations (Lang and Lozano, 1998). A longstanding view is that dopamine depletion in the basal ganglia network caused by PD produces an imbalance in motor selection mechanisms that impedes action selection and initiation (i.e., underactive "direct" pathway of the basal ganglia) but facilitates action inertia or suppression (i.e., an overactive "indirect" pathway of the basal ganglia, Calabresi et al., 2014; Mink, 1996). A curious and somewhat paradoxical finding is that speeded reaction times (RT) of PD patients in simple or choice reaction tasks, which are typically measured in the sub-second range, are often indistinguishable from healthy peers (Bissett et al., 2015; Gauggel et al., 2004). Instead, over the last decade, a robust literature indicates that PD is accompanied by a pronounced reduction in the proficiency of inhibiting action (Praamstra et al., 1999; Wylie et al., 2009a, 2010; for a review, see Dirnberger and Jahanshahi, 2013).

Gauggel et al. (2004) were the first to use the powerful framework

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of the stop-signal paradigm to compare going and stopping latencies of motor responses between PD patients and controls. In the stop-signal task, participants issue speeded choice reactions to a series of "go" signals (e.g., press a left button to left-pointing arrows, and vice-versa for right-pointing arrows). Interspersed randomly into the series of "go" trials are less frequent "stop-signal" trials. On "stop" trials, a go signal appears initially, but then a stop-signal occurs after a brief delay (e.g., the go signal changes color or a tone is sounded), which instructs the participant to try to stop, or inhibit, their go reaction. The timing of the stop-signal presentation after the go signal onset is adjusted dynamically to yield approximately 50% success in stopping initial go reactions on stop trials, an ideal value for applying a set of mathematical operations to estimate an individual's stop-signal RT (SSRT), or response inhibition latency (Logan, 1994; Logan and Cowan, 1984). Gauggel and colleagues reported that mean go RTs were similar between PD and control groups, but PD patients showed significantly longer SSRT, suggesting a focused impairment in the ability to inhibit motor responses.

A handful of subsequent studies have reported on PD performance using variations of the stop-signal paradigm, and some discrepancies exist. Our review of studies that used the standard version of the stop-signal paradigm[1] led to an interesting observation. We identified studies showing intact going coupled with impaired stopping latencies among PD patients compared to controls (Gauggel et al., 2004; Joti et al., 2007; Ye et al., 2014, 2015). In contrast, we also found studies reporting the opposite pattern in PD, namely slower going coupled with intact stopping latencies (Bissett et al., 2015; Vriend et al., 2015). These patterns led us to hypothesize that PD patients experience exacerbated tradeoffs between going and stopping mechanisms. Prioritizing one component of action control (e.g., response going) may cause exaggerated compromise to the other form of action control (e.g., response inhibition). We further hypothesized that dopamine might modulate these tradeoffs.

Unfortunately, no studies of the standard stop-signal paradigm in PD have investigated how dopamine medications affect these processes. Notably, Obeso and colleagues investigated the effects of dopamine medications on PD performance in a conditional stop task, reporting that PD patients were significantly slower at going and stopping to critical stimuli (Obeso et al., 2011). They reported that dopamine state had no effect on either performance measure. One limitation of the conditional stop-signal paradigm, which requires stopping certain "critical" responses but not other "non-critical" responses, is that it violates the assumption of independence between going and inhibition mechanisms that is crucial to the stop-signal paradigm and the underlying race model (Logan, 1994; Logan and Cowan, 1984). For example, mean RT on failed stop-signal trials should be shorter than mean RT on go trials, a criterion that was not satisfied by PD patients in the conditional stop task (Obeso et al., 2011). While this does not detract from other measures reported in the study, it does raise concerns about the reliability of the calculated SSRT. Thus, it remains an open empirical question whether dopamine medication modulates tradeoffs between going and stopping latencies in human PD.

The goal of the current study was to test the hypothesis that withdrawal and administration of dopaminergic drugs modulates the balance between going and stopping of motor responses. We tested a group of 33 PD patients on and withdrawn from dopaminergic medications using a standard stop-signal paradigm with one extension. Instead of instructing participants to merely stop their reactions on stop trials, we asked them to stop their reaction (Bissett and Logan, 2013) and execute an alternative response instead (i.e., a stop-change paradigm; Logan and Burkell, 1986; Verbruggen and Logan, 2009a; van den Wildenberg et al., 2017). This permitted comparison of tradeoffs in the latencies of going, stopping, and changing responses as a function of dopamine state. We tested two competing views about how dopamine depletion in PD should impact going and stopping latencies. According to the classic view, progression of PD shifts the balance of activity along direct (going) and indirect (stopping) basal ganglia pathways, leading to underactive direct pathway and overactive indirect activities and consequent disruption to the speed of going (Calabresi et al., 2014; Mink, 1996). Thus, the dopamine-depleted off medication state should impair the generation of overt motor responses to external signals, reflected by slower going (i.e., longer go RT) and slower changing (i.e., longer change RT). In addition, inhibition latencies are predicted to be in the normal range or enhanced (i.e., normal or shorter SSRT). These patterns would then be expected to reverse with facilitation of dopamine activity. Alternatively, if PD fundamentally alters response inhibition processes (Gauggel et al., 2004; Praamstra et al., 1999; Wylie et al., 2009a, 2010; for a review, see Dirnberger and Jahanshahi, 2013), then in the off dopamine state, going and changing latencies would be normal but stopping would be slowed; stopping latency would then improve with dopaminergic medication.

2. Methods

2.1. Participants

PD participants (n = 33) were recruited from the Movement Disorders Clinics at the University of Virginia and Vanderbilt University medical centers. Healthy controls (HC; n = 21) were recruited from community advertisement or as qualifying family members of PD participants. All participants met the following criteria: no history of neurological condition (besides PD); bipolar affective disorder, schizophrenia, or other psychiatric condition known to compromise executive cognitive functions; or severe and/or untreated mood disorder or medical condition known to interfere with cognition (e.g., diabetes, pulmonary disease). A movement disorder neurologist diagnosed PD. All patients were treated currently with levodopa monotherapy (n = 14), dopamine agonist monotherapy (n = 7), or levodopa plus agonist dual therapy (n = 12). PD motor symptoms were graded using the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore. Additionally, they all received a rating of stage III or less using the Hoehn and Yahr scale (Hoehn and Yahr, 1967). Based on these data, each PD participant was experiencing mild to early moderate symptoms. Dosages for the dopamine medications were converted to levodopa equivalent daily dose (LEDD) values (Weintraub et al., 2006). Individual PD participant characteristics are presented in Supplementary Table 1.

All PD patients performed at a level on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) that ruled out dementia but permitted very mild to minimal gross cognitive difficulties (all scores ≥ 24; M = 27). HC all scored above 26 (M = 28) on the MoCA. All participants reported stable mood functioning and the absence of major depression during a clinical interview, but we allowed endorsements of mild to low moderate symptoms of depression on the Center for Epidemiological Studies Depression (CES-D) questionnaire (mean CES-D: HC = 7; PD = 14). As described in the Results section, neither depression nor mental status scores was related to the primary experimental task performance measures. All participants had corrected-to-normal vision. They all provided informed consent prior to participating in the study in full compliance with the standards of ethical conduct in human investigation as regulated by the University of Virginia and Vanderbilt University.

2.2. Experimental task and procedures

Participants completed the stop-change task (see Fig. 1) in which left- and rightward pointing arrows were presented, one at a time, on a

[1] As opposed to variations involving selective or conditional stopping manipulations, which may be violating assumptions underlying the horse-race model calculation of SSRT (see Band et al., 2003).

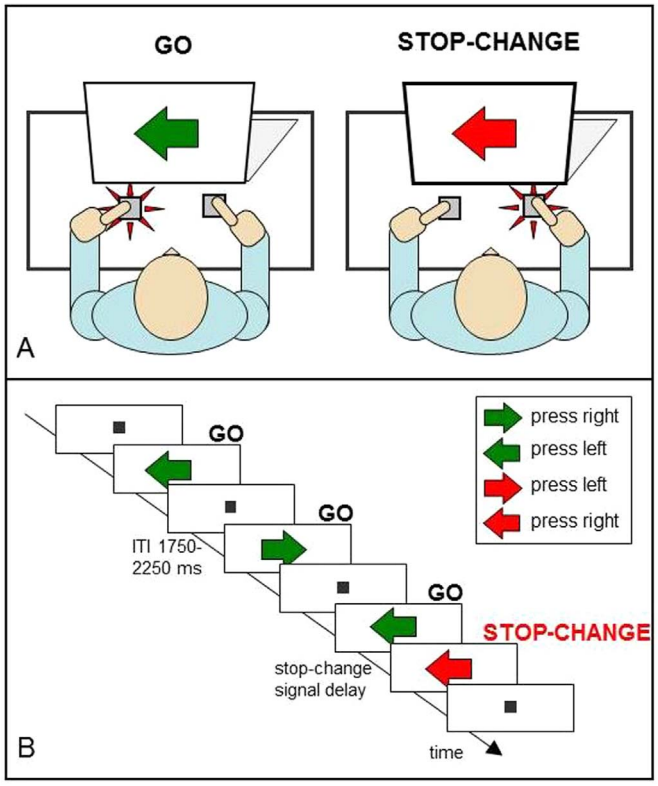

Fig. 1. Stop-Change Task. Participants were instructed to press the left or right button in the direction indicated by the green arrow (i.e., go trials). On 30% of the trials, the color of the arrow changed from green to red (i.e., stop-change trials) upon which participants should inhibit the go response and execute the alternative response. Upon presentation of the stop-change signal in this example, participants should inhibit the left-hand response and execute the right-hand response instead.

17-in. digital display monitor placed at a distance of about 90 cm and positioned such that each arrow appeared at eye level. The go signal was a green arrow shown at visual fixation against a white background. It consisted of a rectangular stem (2.1 × 2.1 cm) attached to a triangular arrowhead (1.5 cm height × 2 cm base). Each block of trials began with the appearance of a small fixation square (.8 cm height × width, subtending a visual angle of .46°) at visual fixation that was displayed continuously on the screen in between arrow presentations until the block ended. Trials were separated by a variable interval that ranged randomly from 1750 to 2250 ms in increments of 50 ms. The arrows were presented pseudo-randomly, with the constraint that left- and right-hand responses were signaled equally often on both go and stop-change trials. The arrow was extinguished following the participant's response, consisting of a left or right thumb press on a response button located at the end of a grip held comfortably in each hand, or after a time limit of 1500 ms had passed.

Participants were instructed to respond as quickly as they could to go signals while trying to maintain an accuracy level of 90–95%. Instructions specified that participants should make a thumb press corresponding to the direction in which the green arrow pointed (e.g., ⬅, left button press). On 30% of trials, identified as *stop-change trials*, the arrow turned from green to red after a brief, variable delay. Whenever this color change occurred, participants were instructed to stop the hand response signaled by the direction of the initial green arrow and instead to quickly execute an opposite hand response. For example, if a green arrow pointing to the right appeared but then changed to red, the participant should stop the preparation of the right hand response and press the left button instead. Because of the possible lateralization of motor symptoms in PD patients, two independent staircase-tracking procedures were implemented for left- and right-hand stop-change trials that dynamically adjusted the interval between the onset of the go signal and the onset of the stop-change signal (i.e., the stop-change signal delay) on the next stop-change trial (Levitt, 1971). After a successful change, the stop-change signal delay was increased by 50 ms, making it more difficult to change on the next stop-change trial. After a failed change (i.e., the go response was given or the go response was stopped but the change response was not given), the delay was decreased by 50 ms making it easier to change. The tracking algorithms ensure that approximately half of the motor actions are changed successfully so that the most accurate estimates of the SSRT can be derived (Band et al., 2003). Importantly, these tracking algorithms permit stop-change signal delays to be estimated for each response hand of each participant and, in so doing, control for individual differences in both overall response latency and in response latencies to the go signal between the two hands. Participants completed five blocks of 104 trials, the first of which served as a practice block. Thus, the data acquisition blocks yielded 146 trials for each response direction on the go trials and 62 trials for each response direction on the stop-change trials.

HC participants completed just one session of the stop-change task. PD participants completed two sessions, once while taking all of their prescribed dopaminergic medications in their optimal "on" phase of their medication cycle, and a second time following a 24–48 h withdrawal from dopaminergic medication. Patients taking Levodopa were withdrawn for a minimum of 12 h and up to 24 h depending on the time of testing and medication schedule. Because dopamine agonists have a longer half-life, we extended the washout to a minimum of 48 h (see also van Wouwe et al., 2016). The order of visits was counterbalanced across PD participants and completed at approximately the same time of day. Importantly, no changes in medication dosages or addition or discontinuation of dopamine medication for clinical purposes were made at any time during study participation.

2.3. Data analyses

SSRT to stop-change signals was estimated using the integration method (Logan, 1994; Logan and Cowan, 1984) that is more robust to common SSRT contaminants like skewing and response slowing than other estimation methods (Verbruggen, Chambers, and Logan, 2013). Stop-signal tracking based on inhibition rates of approximately 50% generally provides reliable SSRT estimates (e.g., Band et al., 2003). Finally, the latency required to issue the change response (i.e., change RT) was calculated by subtracting change-signal delay from the RT to execute the alternative response.

The key dependent measures were mean go RT on correct trials, SSRT, and change RT on correct trials. Since none of the dependent measures differed significantly between left and right hand responses (all $ps > .10$), data were collapsed across hands. Percentages of commission and omission errors on go trials, RT on failed change trials, and percentage stop-change success on stop-change trials were also computed and analyzed to check key assumptions of the underlying race model (Logan, 1994). Percentages of choice errors on go trials and of change success on stop-change trials were square root transformed before analyses. Our first set of analyses used repeated-measures ANOVAs and independent samples *t*-tests as appropriate to compare PD patients in their off dopamine state with HC across the key dependent measures. Next, we used paired samples *t*-tests to compare the effects of *Dopamine State* (Off vs. On) within the PD group on key dependent measures. Because performing multiple tests increases the probability of committing a type I error, alpha was lowered from .05 to .025. A final analysis used Pearson correlations (with *p*-value adjustments for multiple comparisons) to test the relationship between changes in go RT and SSRT between dopamine states.

To provide additional quantification of the strength of our findings (Wagenmakers, 2007), the main hypotheses were also examined by calculating a Bayes factor (Jarosz and Wiley, 2014; Rouder et al., 2009;

Table 1
Sample characteristics.

	HC	PD
Sample size (N)	21	33
Gender (M:F)	9:12	20:13
Age (years)	61.5 (5.4)	63.5 (6.1)
Education (years)	16.4 (2.6)	15.5 (2.2)
MoCA	28.0 (1.4)	26.8 (1.9)
AMNART	122.3 (4.9)	120.3 (5.8)
CES-D*	7.1 (7.2)	14.2 (7.7)
LEDD	–	698 (437)
Years since onset	–	5.0 (2.2)
Years since diagnosis	–	3.5 (2.4)
UPDRS diff	–	12.6 (10.9)
Initial symptom onset (N)		Right: 17 Left: 14 Bilateral: 2

Standard deviation in parentheses; * $p < .05$.
MoCA = Montreal Cognitive Assessment; AMNART = American modification of the National Adult Reading Test; CES-D = Center for Epidemiological Studies-Depression Scale; LEDD = Levodopa Equivalent Daily Dosage; UPDRS diff = Unified Parkinson's Disease Rating Scale, Motor score improvement On vs Off medication.

Wetzels et al., 2012). The Bayes factor (BF_{01}) provides the odds ratio for the null versus the alternative hypotheses given a particular data set. We used JZS Bayes Factor with r = .707 as recommended by Rouder et al. (2009).

3. Results

3.1. Analysis of sample demographics

Table 1 shows that HC and PD groups were similar in age, education (all *t*-tests yielded *p*s > .05), and gender distribution, $\chi^2(1, N = 54) = 1.63$, $p = .20$.

3.2. PD Off medication vs. HC

3.2.1. Go RT

See Table 2 for an overview of dependent behavioral variables. PD patients Off of their dopaminergic medication and HC responded to go signals (see Fig. 2) with similar response latencies (PD Off = 563 ms, HC = 607 ms; *Group*: $t(52) = 1.41$, $p = .17$; $BF_{01} = 1.59$ in favor of null hypothesis). The Bayes factor suggested a roughly 1.6:1 odds in favor of the null hypothesis of no difference between the two groups. Go responses of both groups were comparable in terms of choice error rates (PD Off = 4.4%, HC = 2.4%; *Group*: $t(52) = 1.64$, $p = .11$; $BF_{01} = 1.46$).

3.2.2. SSRT

The tracking algorithm worked well and converged to successful change percentages near 50% for both groups (PD Off = 51%, HC = 52%; *Group*: $t(52) = .51$, $p = .62$). SSRT (see Fig. 3) was prolonged significantly among PD Off (261 ms) compared to HC (228 ms; *Group*: $t(52) = 2.61$, $p = .01$; $BF_{01} = 4.22$ in favor of alternative hypothesis). The Bayes factor provided substantial support for the alternative hypothesis of a difference in SSRT among the groups. Go RT did not correlate with SSRT in either group (PD Off: $r = -.26$, $p = .14$ vs. HC: $r = .20$, $p = .40$). The prolongation of SSRT among PD Off patients compared to HC was preserved even with go RT included as a covariate, $F(1, 54) = 5.81$, $p = .02$. Also consistent with the race model, RT on failed change trials (i.e., RTs to the initial go signal that escaped inhibition) were shorter than the overall mean go RT (respectively 508 ms vs. 585 ms; *Trial Type*: $F(1, 52) = 193.26$, $p < .001$). Both groups showed this pattern, although this difference was larger among HC than for PD Off (97 ms vs. 56 ms; *Group x Trial Type*: $F(1, 52) = 13.87$, $p < .001$).

Table 2
Dependent behavioral variables.

	HC	PD Off	PD On
Go RT	607 (118)	563 (108)	621 (138)
Choice errors (%)	2.4 (1.6)	4.4 (4.3)	3.8 (3.9)
Stop-change signal delay	343 (110)	272 (117)	342 (146)
Failed Change RT	510 (87)	507 (87)	537 (106)
Successful stop-change (%)	52 (4)	51 (6)	53 (6)
SSRT	228 (38)	261 (48)	241 (60)
Change RT	583 (83)	575 (94)	593 (96)

Standard deviation in parentheses.

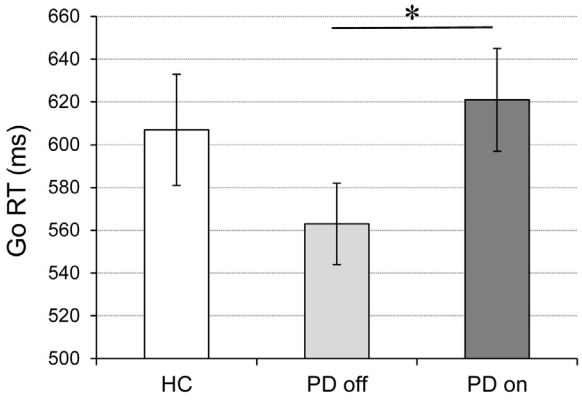

Fig. 2. Mean reaction time (RT) to go signals for healthy controls (HC), patients off (PD Off), and on medication (PD On). Error bars represent standard errors. * $p < .05$.

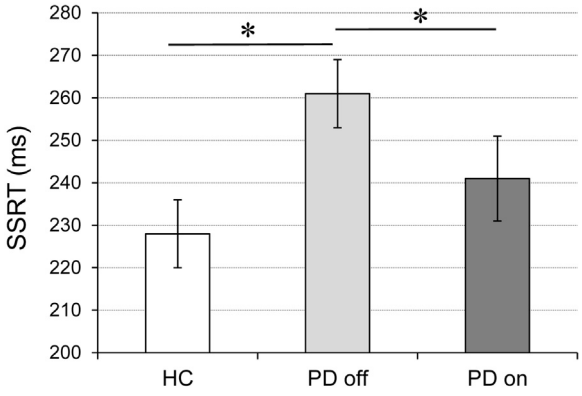

Fig. 3. Mean stop-signal reaction time (SSRT) for healthy controls (HC), patients off (PD Off), and on medication (PD On). Error bars represent standard errors. * $p < .05$.

3.2.3. Change RT

The latency to change and to issue the alternative response on successful change trials (see Fig. 4) was similar between PD Off and HC (575 ms, 583 ms, *Group*: $t(52) = .33$, $p = .75$; $BF_{01} = 3.41$ in favor of null hypothesis).

3.3. PD Off versus on medication

3.3.1. Go RT

Responses to go signals were significantly slower (Off = 563 ms, On = 621 ms; *Dopamine State*: $t(32) = 3.38$, $p = .002$; $BF_{01} = 18.13$ in favor of alternative hypothesis), but equally as accurate when PD patients performed in the active dopamine medication state compared to withdrawn from dopamine medication (error percentages: Off = 4.4%, On = 3.8%; *Dopamine State*: $t(32) = 1.32$, $p = .20$; $BF_{01} = 2.43$ in favor of null hypothesis). Bayes factor provided strong evidence in favor

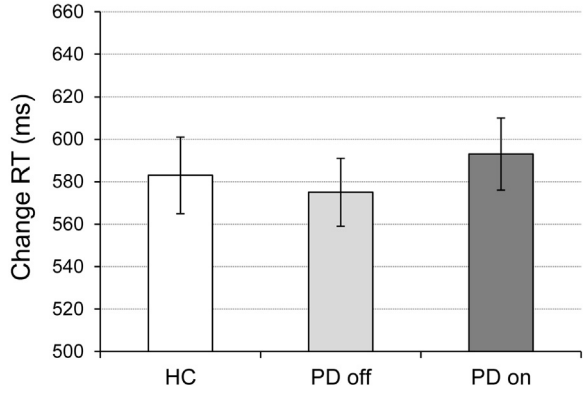

Fig. 4. Mean reaction time (RT) to the change signal for healthy controls (HC), patients off (PD Off), and on medication (PD On). Error bars represent standard errors.

of the alternative hypothesis that latency of go reactions differed between medication states.

3.3.2. SSRT

The tracking algorithm worked well and converged to successful change percentages that approximated 50% across dopamine states (Off = 51%, On = 53%; *Dopamine State*: $t(32) = 1.82$, $p = .08$). SSRT was significantly shorter in the dopamine active state compared to dopamine withdrawn (On = 241 ms, Off = 261 ms; *Dopamine State*: $t(32) = 2.48$, $p = .02$; $BF_{01} = 2.59$ in favor of alternative hypothesis). Bayes factor provided anecdotal support for the alternative hypothesis of a difference in SSRT due to dopamine medication state. In line with the predictions and critical assumptions of the race model, RT on failed change trials (i.e., those that escaped inhibition) was shorter than overall mean go RT (522 ms vs. 592 ms; *Trial Type*: $F(1, 32) = 95.48$, $p < .001$). The same pattern of shorter failed change RT compared to mean go RT was also preserved across dopamine states, although the difference was larger in the active dopamine state compared to the Off dopamine state (84 ms vs. 56 ms, *Trial Type* × *Dopamine State*: $F(1, 32) = 14.78$, $p < .001$).

3.3.3. Change RT

Correct responses to change signals were executed with similar mean response latencies in dopamine withdrawn and active dopamine states (Off = 575 ms, On = 593 ms; *Dopamine State*: $t(32) = 1.15$, $p = .26$; $BF_{01} = 2.93$ in favor of null hypothesis).

3.4. Associations between medication effects on go RT and SSRT

Given the effects of dopamine state on go RT and on SSRT, we computed the correlation between changes in both measures by contrasting performance in the withdrawn and active dopamine states. This produced a negative correlation, ($r = -.40$, $p = .02$), indicating that changes in go RT from withdrawn to active dopamine states were accompanied by opposite effects on SSRT (see Fig. 5). This indicates that more pronounced slowing of go RT induced by active dopamine was associated with shorter SSRT, i.e., more proficient stopping.

4. Discussion

We studied the effects of PD and dopaminergic medication on three components of speeded action control: going, stopping, and changing of motor responses. Previous studies reported a deficit in either going or stopping latencies in PD compared to HC (see Section 1). Only a few studies investigated the effects of dopamine medication on these processes concurrently. We observed that dopamine modulates the tradeoff between going and stopping in PD.

Compared to HC, PD patients in the off dopamine state showed

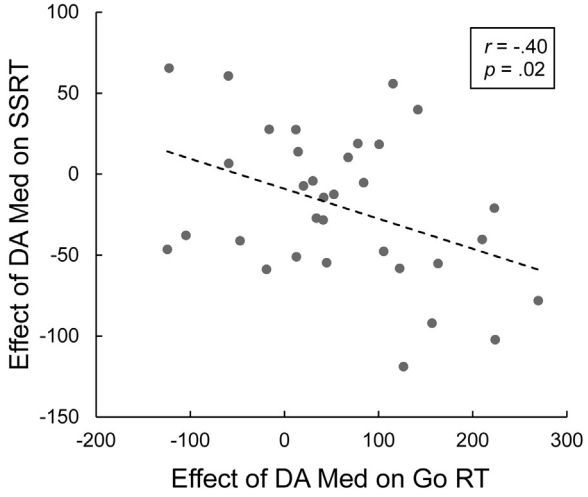

Fig. 5. Negative correlation between the effects of dopaminergic medication on going (Go RT) and stopping (SSRT) in ms. Positive values indicate slowing, negative values indicate speeding of RT with dopaminergic medication. PD participants exhibiting more pronounced slowing of go RT induced by active dopamine had shorter SSRT compared to their Off state.

normal go and change latencies, but were significantly slower to inhibit responses. This conforms to an emerging literature suggestive that inhibitory motor control deficits are a central feature of PD (Gauggel et al., 2004; Mirabella et al., 2017; Praamstra et al., 1999; Wylie et al., 2009a, 2010; for a review, see Dirnberger and Jahanshahi, 2013). Although PD patients in the off medication state were able to maintain response latencies in the same range as HC, this was accompanied by significant reductions in the ability to stop reactions abruptly. In contrast, performance of PD patients shifted significantly when taking their dopaminergic medications. Specifically, going slowed, but stopping improved relative to the off dopamine state. Moreover, the magnitude of response slowing from off to on dopamine states correlated with the magnitude of improved inhibition latencies from off to on dopamine states. This pattern suggests a role for dopamine in modulating the tradeoff between the two action control processes. Interestingly, the latency of the change response (i.e., change RT) was comparable between HC and PD groups, and did not vary with medication state. These null effects with respect to changing latencies are notable when taking into account the prolongation of going latencies observed with medication. Apparently, PD patients on medication are able to change their responses as proficiently as during their off state, but this effort seemingly occurs at the expense of prolonged going latency. In essence, the observed dissociation between medication effects on going vs. changing further corroborates the notion of a tradeoff between prioritizing speeded responding (i.e., going) versus prioritizing control over that response (i.e., stopping and changing that response).

4.1. Effects of dopamine on going versus stopping

At first glance, the patterns reported here seem somewhat at odds with the conventional model of how dopamine depletion in PD and dopamine restorative therapy impact action selection and inhibition systems expressed, respectively, along direct and indirect basal ganglia pathways. According to the classic model, dopamine depletion in PD produces under-activity along the direct pathway, leading to slow response selection and initiation, but over-activity along the indirect pathway, leading to excessive motor inhibition. The net effect is difficulty selecting and activating desired motor actions. Dopamine-facilitating medications restore the balance. However, the current findings add to an emerging literature that PD fundamentally disrupts the ability to inhibit already initiated or unwanted prepotent action tendencies while often leaving the proficiency in speeded responding to go signals

uncompromised. The current findings are consistent with other studies suggestive that dopamine improves inhibitory control deficits in PD (van Wouwe et al., 2016; Wylie et al., 2012).

The patterns observed here are suggestive that isolating the effects of PD and of dopamine medication on a specific action control process (e.g., either going or stopping) fails to capture the dynamic tradeoffs between these processes. The current findings suggest that it may be more accurate to conceptualize the effects of PD and dopamine on the coordination of action control processes rather than on their isolated efficiencies. Action selection/initiation and action control/inhibition represent dynamic modes of control that can be coordinated and strategically toggled to meet the demands of the situation (Bissett and Logan, 2011; Bissett et al., 2015; Mirabella et al., 2006; Tolleson et al., 2017). The natural tradeoff between going and stopping in the healthy brain is exacerbated in PD such that prioritizing going leads to even more pronounced reductions in stopping control, but prioritizing stopping control (i.e., inhibition) produces even greater slowing of responses in PD compared to controls (van Wouwe et al., 2014; Wylie et al., 2009b). Similar tradeoffs in going and stopping are reported in studies of healthy adults in which experimental factors shift prioritization of going or stopping (Federico and Mirabella, 2014; Verbruggen and Logan, 2009b).

The current findings accord with recent patterns in PD involving tradeoffs between response latency and the ability to suppress impulsive action tendencies during response conflict, such as on incongruent trials on the Simon task (van den Wildenberg et al., 2010). When PD patients are pressured to prioritize speed of responding, they show similar speeding as HC but exacerbated deficits in their ability to suppress interference from incorrect response impulses (van Wouwe et al., 2014; Wylie et al., 2009b). In contrast, this tradeoff is partially restored when patients are instructed to prioritize preventative control over response errors (i.e., prioritize response accuracy). Adding to this story are studies showing that cognitive control mechanisms involved in making speed-accuracy adjustments in performance involve frontal-basal ganglia circuitries (Forstmann et al., 2008a, 2008b; Huang et al., 2015; Jahanshahi et al., 2015). The work here suggests that tradeoffs between these modes of action control may be critically modulated by dopamine. More specifically, dopamine appears critical for supporting shifts toward prioritizing inhibitory control mechanisms as opposed to promoting fast responding (see also van Wouwe et al., 2016). Recent imaging work in mild to moderate PD patients showed that administration of dopaminergic medication improved motor performance and reduced pathologically increased putamen–cerebellar functional connectivity to levels that were comparable to the healthy control group (Simioni et al., 2016). These findings are relevant since recent imaging work with healthy adults suggested that the cerebellum might be critically involved in inhibitory motor control (Hirose et al., 2014).

The present findings complement pharmacological studies showing that dopamine modulates action control in healthy participants. Ramdani and colleagues showed that consuming an amino acid mixture that selectively reduces dopamine precursor levels, impaired impulse suppression in a spatial Simon task (Ramdani et al., 2015). More specifically, dopamine depletion was associated with less proficient suppression of impulsive action tendencies in the electromyogram. In addition, correct trials with longer RTs were associated with increased interference effects. Interestingly, dopamine depletion did not alter overall response latencies. This dissociation between going and stopping mechanisms was also observed by a pharmacological study by Colzato and colleagues using a stop-signal paradigm. Compared to a placebo condition, the intake of tyrosine (which enhances dopamine release) improved stopping but did not affect response latencies (Colzato et al., 2014). Furthermore, healthy participants with a genetic predisposition associated with relatively higher striatal DA levels showed prolonged stopping latencies and scored higher on a self-report questionnaire measuring dysfunctional impulsivity (Colzato et al., 2010; see also Congdon et al., 2009; Cummins et al., 2012).

What remains unclear is how dopamine modulation (e.g., on vs. off medications) interacts with mechanisms underlying strategic adjustments between going and stopping. For example, can PD patients prioritize inhibitory control to normal levels in the off dopamine state, and at what cost to response latency? Insight into this question comes from a recent functional imaging study of stop-signal task performance in *de novo* PD patients (Vriend et al., 2015). In comparison to HC, PD patients showed intact response inhibition latencies (SSRT), but at the cost of prolonged go latencies. Moreover, de novo PD showed reduced activation of the right inferior frontal cortex on stop-signal trials, consistent with reductions in circuitry linked to inhibitory control (Aron et al., 2007; see also Ye et al., 2014). Thus, PD patients appear capable of making adjustments in modes of control to overcome a deficient inhibitory control system. A similar form of motor adjustment was reported recently in PD patients performing a response conflict task under speed pressure (van Wouwe et al., 2014). In situations involving conflict from an impulsive action tendency, PD patients' EEG showed reduced physiological inhibition of the motor cortex controlling the impulsive motor response, but a compensatory exacerbation of activation of motor cortex controlling the correct motor response. Thus, a critical question for future studies is determining whether tradeoffs and shifts in going and stopping mechanisms are a direct consequence of the neurophysiology of PD and dopamine or related to compensatory effects in response to deficits in either going or stopping mechanisms directly. One interesting possibility would be the demonstration that action generation circuitry and response inhibition circuitry are disproportionately active in off and on dopamine states and correspond to the prioritization of either action control mode.

4.2. Clinical implications and limitations

Conceptualizing the impact of PD and dopamine medications on tradeoffs and coordination of going versus stopping control mechanisms has potential clinical and therapeutic implications. One implication is that improvements in motor control due to dopamine medication may be related to better inhibitory motor control as opposed to speeding the initiation or selection of actions. Most movements captured in the clinic represent complex movements and movement sequences that involve starting, stopping, and changing multiple actions and action sequences. While performance on complex motor tasks presents as slower in PD (i.e., bradykinetic), this slowing might result from poor inhibition and control of actions over the course of the motor sequence rather than initiating individual actions. In fact, despite slower inhibition of an ongoing action, the latency to execute an alternative action (change RT) was similar in PD patients off and on their dopamine medications. Thus, the beneficial effect of dopamine to inhibition (versus the effect of dopamine on going or changing responses) may be the key factor in improving speed of coordinated action sequences.

Another application of the action control tradeoff notion was recently described in a study of stop-signal task performance in dopamine-medicated PD patients with and without freezing of gait (FOG) symptoms (i.e., sudden arrests in ambulation) relative to HC (Bissett et al., 2015). That study included a condition in which participants issued responses to go trials without interspersed stop trials (i.e., a block of pure go trials). This allowed measurement of strategic, proactive slowing of responses in another context that required the occasional but unpredictable need to stop action abruptly (i.e. in a classic stop-signal task). Both patient subgroups slowed their go responses twice as much as HC, indicative of pronounced proactive slowing. Patients with FOG showed longer SSRT compared to patients without FOG. Stopping latencies of the latter subgroup did not differ from HC. Apparently, medicated PD patients without FOG can tradeoff go speed for stopping speed, given large proactive slowing. Thus, certain clinically relevant symptoms in PD may predispose to even greater tradeoffs between going and stopping, neither of which can be prioritized concurrently to normal levels. Future studies might include a

block of go trials without interspersed stop-signal trials, to study how a stopping context impacts on strategic adjustments in going and stopping during off and on dopamine medication states. Indeed, Mirabella et al. (2013, 2017) have demonstrated that PD disrupts proactive control processes and that deep brain stimulation modulates these context effects.

Studying the effects of individual differences in PD could further unlock important neurophysiological mechanisms underlying action control tradeoff effects. The impact and direction of dopaminergic changes on cognition is known to vary between individuals (Cools, and D'Esposito, 2011). An inverted "U" shaped curve describes this relation, hypothesizing that shifts in dopamine levels can either improve or deteriorate cognitive functions based on individual baseline dopamine state (Cools, 2006; Cools et al., 2001). Several clinical studies used this model to explain observed individual differences in dopamine medication effects on inhibitory action control between PD patients (e.g., Costa et al., 2014; van Wouwe et al., 2016; Wylie et al., 2012). Future clinical studies might focus on individual differences with respect to shifting the balance between going and stopping motor responses. Additionally, dopamine is proposed as a key modulator in mechanisms that code the costs/effort relative to the benefits/reward of movement (Mirabella, 2014). Future investigations would also benefit from examining how shifts in going and stopping are influenced by variations in the effort or rewards associated with these modes of action control (Mazzoni et al., 2007; Tinaz et al., 2016).

A limitation of the current study was that we only measured the effects of short-term withdrawal from dopaminergic medications. Thus, it remains an open empirical question how longer washout periods or comparison between a *de novo* state and a medicated state may have influenced patterns of effects reported here. Chronic dopaminergic medication use is linked to specific changes in dopamine receptor density and sensitivity (LeWitt, 2015; Riverol et al., 2014), which cannot be fully appreciated in the current study.

4.3. Conclusion

In summary, we report a significant tradeoff between going and stopping in PD patients that is modulated by dopamine state. Dopamine facilitation in PD shifts performance control toward slower responding to the benefit of inhibitory control.

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Disclosure statements

There are no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.12.032.

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